REVIEW PAPER

Impact of Ghrelin and Adiponectin on Metabolic and Cardiovascular Effects

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Abstract

Background: Ghrelin and adiponectin are recently discovered peptides. Ghrelin has a crucial role in the regulation of food intake and energy homeostasis, and adiponectin is secreted by adipocytes, and it has been proposed to mediate obesity-related insulin resistance. Both they are playing a critical role in a variety of physiological processes including endocrine, metabolic, cardiovascular, and other actions. Furthermore, other potential clinical applications of ghrelin include the treatment of patients with diabetes mellitus and infections, likewise adiponectin plays an important role in diagnosis of cardiovascular disease.
Conclusions: Further studies need to specify the accurate results and the action mechanisms of adiponectin in order to facilitate the clinical practice; as well as to clarify the role of these adding a new knowledge in international scientific community.

Key Words: Adiponectin, Ghrelin, peptides, obesity, cardiovascular disease

Introduction

Ghrelin is a recently discovered hormone, with a crucial role in the regulation of food intake and energy homeostasis (Korbonits et al, 2004). Ghrelin levels increase before meals and decrease after meals. It is considered the counterpart of the hormone leptin, produced by adipose tissue, which at higher levels induces satiation. In some bariatric interventionalprocedures, the level of ghrelin is reduced thus causing satiation before it would physiologically occur.

Adiponectin lipokines are hormones produced by the adipose tissue. They were detected in early of 90s, and leptin was the first member of the family been discovered. Before this discovery, the adipose tissue was known as energy store compartment regulating lipid metabolism and thermogenesis. Adiponectin is an approximately 30-kDa polypeptide, and interestingly, the terminal structure of its globular domain bears a striking similarity to tumor necrosis factor-α (TNF-α), despite a lack of homology intheir primary sequence (Shapiro & Scherer, 1998).

After briefly reviewing the physiologically relevant effects of the two adipose tissue mediators we focused on the potential mediating mechanisms with pathophysiological importance on metabolic and cardiovascular disease initiation and progression.

Ghrelin

Few peptide hormones have attracted as much attention as ghrelin, the natural secretagogue for growth hormone (GH) identified by Kojima et al in 1999, resulting >4000 PubMed citations over the last ten years (Kojima et al, 1999). It was initially observed that ghrelin could stimulate feeding in mammals, and may have clinical implications on the development of antiobesity drugs. Subsequent studies revealed the complexity of the ghrelin modulated mechanisms including the differential physiological effects of the three peptide products of the ghrelin gene: ghrelin, which is peri-translationally modified via acylation with the octanoic acid; des-acyl ghrelin(molecule not-acylatedor orphan from its fatty acid residue); andobestatin, another bioactive peptide derived from the pre-proghrelin precursor (Fetissov et al, 2010).

Ghrelin is abundantly synthesized by specialized mucosal cells in the stomach accounting for about 80% of the serum ghrelin production in rats and for 65% in humans. Some ghrelin producing cells are also found in lower parts of the gastrointestinal (GI) tract, where ghrelin expression could be up-regulated in special circumstances (e.g. after gastrectomy). Low circulating levelsof ghrelin are associated with obesity, insulin resistance and diabetes mellitus type 2 (Sakata et al, 2010; Veldhuis & Bowers, 2010).

Most importantly, it has beenpostulatedthat beyondstimulation of growth hormone (GH) secretion and increased feeding, ghrelin has multiple biological effects. Over these functions, ghrelin was found to regulate gastrointestinal motility, sensory functions, reproduction, psychical sphere, glucose metabolism, cardiovascular system and kidneyfunction (Meyer, 2010; Schwandt et al, 2010).

Adiponectin

Adiponectin or liponectine was detected in 1995, by four independent research teams (Badman & Flier, 2007). It was determined initially in mice as a protein expressed in 3T3-L1 adipose cell-line, and lateron as an exclusive product of the adipocytes' gene apM1 (Maeda et al, 1996; Asmundsdottir et al, 2002). Adiponectin is a molecular weight 30 kDa protein which is produced elusively in white adipose tissue, although some reports describe also its expression in grey matter adipose tissue in T37i cellular line (Roilides et al, 2004).The molecule of human adiponectin consists of 247 amino-acid residues. Each unilateral of adiponectin, presents 4 distinct regionsin a row: the amino-terminal end of protein, a variable region, the region with sequence proportional to collagen and the terminal end of spherical carboxyl (Berg et al, 2002; Pajvani et al, 2003).

The structure of adiponectin receptors was recently detected and both its isomers were determined. The first adiponectin's receptor (AdipoR1) is mainly expressed in lineate muscles, whereas its second receptor (AdipoR2) is mainly expressed in the liver (Krcmery & Barnes, 2002).

Adiponectin acts via connection of its molecule with the special adiponectin receptors on cells surface in the main target organs: muscles, liver and vessels (Chandran et al, 2003). The most important adiponectin functions so far, are reflected through its antiathero-genetic, anti-inflammatory and tissue insulinsensitizing action (Torres et al, 2005).

As concerns the anti-inflammatory effect, it was shown that both TNFα and adiponectin act at the same target organs with opposing effects (Schoelson et al, 2006; Tilg & Moschen, 2008). The resultingimbalance can lead to insulin resistance and perpetuation of low grade systemic inflammation (Hotamisligil et al, 1995).

As a sensitizing factor of insulin, adiponectin is linked to special membrane receptors promoting phosphorolysis of acetyl-co-

enzyme a carboxylase, promoting the anaerobic glycolysis and the oxidation of fattyacids (Yamauchi et al, 2002). Additionally strengthens insulin action at the liver, with beneficial effects on both glycaemia and lipaemia (Thamer et al, 2002; Gressner et al, 2007; Ban & Twigg, 2008; Kamada et al, 2008).

Dingetal showed that adiponectin acts inhibitory for the action of the activating asteroid cells and therefore, to the fibrogenesis process in hepatic parenchyma (Ding et al, 2005). This antifibrotic action at hepatic level it might be processed via inhibition of the connective tissue.

Correlation between adiponectin/ghrelin and growth hormone (GH)

Ghrelin and its receptors are produced in almost all tissues including hypothalamus arcuate nuclei, pituitary and placenta (Pomboet al, 2001; Broglio et al, 2003). Ghrelin affects GH secretion and it was initially locatedin the stomach as a ligand for growth hormone secretagogue (GHS) receptor. Additionally, ghrelin exerts direct and indirect modulation in food intake and energy expenditure.

GH produced and secreted by the anterior lobe of the pituitary, promotes the indirect and along increase connected with its receptor in liver through the production of the insulin –like growth factor (IGFI). It has been proved that ghrelin participates with the GHRH (Growth hormone releasing hormone) and the somatostatin to the regulation of the GH production in the pituitary. Ghrelin stimulates direct GH release in vitro from somatotrophs and also when infused in vivo, although the latter action appears to require the participation of an intact GHRH system. Ghrelin stimulates GH secretion in a synergistic fashion when co-infused with GHRH. Experimental, in vivo and in vitro studies demonstrated strong and dose-dependent effect of ghrelin on GH secretion (Broglio et al, 2001).

In humans GH response to ghrelin resists to the external administration of somatostatin or cortistatin. Sex-independent GH and GHS secretion by Ghrelinis progressively diminished with aging, and it is increased bypharmaceutical doses of estrogen (Seoaneet al, 2000; Whatmore et al, 2002).

It was shown that GH treatment in pre-pubertal children decreases serum adiponectin levels, further correlated to the growth response. In a step further, GHD **(**Growth Hormone Deficiency) in adolescence is associated with low adiponectin levels and unfavorable lipid metabolism (Lanes et al, 2006). Adiponectin levels are significantly lower in patients with adult GHD than in patients with acromegaly (Fukuda et al, 2004). Adiponectin concentration did not differin patients with GHD and healthy controls, whereas in patients with acromegaly insulin resistance appears to be not closely related to adiponectinemia in dependently of BMI. The different relationship between adiponectin and quantitative insulin sensitivity check index (QUICKI) observed in adultswith either GHD or acromegaly presumablyreflects differences in the mechanisms of insulin resistance under states of GH deficiency or excess (Andersson et al, 2009).

Effects of ghrelin and adiponectin on glucose metabolism

Clinicalstudies were conducted in order to study ghrelin's action on glucose metabolism and insulin secretion. However, they didn't reach to safe conclusion, due to the ghrelin's different actions(sedative and inhibitory action) to insulin secretion.

Oral glucose tolerancetestingwas accompanied by significant suppression to the increasing insulin levels after ghrelin's administration. Thus, it seems that ghrelin inhibits rapidly insulin secretion in humans after intravenous injection, despite high glucose levels and by contrastinsulin inhibits ghrelin's secretion independently of body adiposity. However, co-administration of ghrelin and antagonist of the GH receptor resulted in an increase of insulin resistance (Kojima et al, 1999; Murdolo et al, 2003; Meyer, 2010).

To date, the role of ghrelin in the regulation of insulin secretion remains controversial, possiblybecause of differences in the experimental conditions. Indeed, ghrelin was found to inhibit insulin secretion in the

majority of the studies but alsoto stimulate insulin secretion in others. For example, ghrelin increased cytosolic free Ca^{2+} concentrations in rat β-cells and increases insulin secretion in isolated rat pancreatic islets under hyperglycemic conditions. Furthermore, ghrelin increases insulin secretion from the pancreas of both normal and diabetic rats. In contrast, GHS-R1a blockade by specific antagonists or ghrelin inactivation using an antiserum enhanced glucose-induced insulin release and intracellular Ca^{2+} concentrations in isolated rat islets.Further, exogenous ghrelin decreased insulin secretion in isolated mouse pancreata, in mouse and rat isolated islets, and in β-cell lines (Kahn & Flier, 2000; Holdstock et al, 2003; Gauna et al, 2004; Heppner et al, 2011).

The findings by Tong et al. provide clear proof of concept that ghrelin can reduce glucose-stimulated insulin secretion. Admittedly, it is possible that ghrelin, due to its local synthesis and release within the islets of Langerhans, may reach very high concentrations at the β-cell and act via an autocrine and/or paracrine rather than systemic mechanisms. Furthermore, although not observed by Tong et al., ghrelin has been found to increase plasma epinephrine levels in humans, suggesting that it may also inhibit insulin secretion via a sympathetic response (Tong et al, 2010).

Ghrelin's action in insulin it has been alsostudied in hepatocytes inhuman. It was observed that ghrelin was activating the insulin receptor type 1 (IRS1) demonstrating that ghrelin has a direct anti- insulin effect, but indirect effect in gluconeogenesis.

Finally, ghrelin has a direct effect to glucose levels, leading to hyperglycemia. Intravenous injection of ghrelin increases glucose levels in humans (obese and individuals with normal weight). Ghrelin administration was accompanied by increased glucose levels not by reduction of insulin because hyperglycemia anticipates hypoinsulinemia by 15 min (Sun et al, 2007). In conclusion, despite conflicting views for ghrelin's action in both insulin release and homeostasis, glucose levels are modulated via: GH release, cortisol, adrenaline, and probably glucagon; enhancementof insulin resistance; activation of gluconeogenesis.

Studies conducted in guinea pigs and later in humans showed are verse relationships between adiponectin and insulin resistance.

There after numerous studies were performed to specifically investigate the correlation between adiponectin levels and metabolic syndrome components including sleep apnea syndrome (Tschritter et al, 2003; Iwashimaet al, 2004; Nagao et al, 2005; Farvid et al, 2005).

Accordingly, low adiponectin levels were detected in patients with type 2 diabetes mellitus (Spranger et al, 2003; Yamauchi et al, 2003), dyslipidemia (Farvid et al, 2005), hypertension, and cardiovascular disease compared to their healthy counterparts (Adamczaket al, 2003; Iwashima et al, 2004).

Gene apM1 was found in chromosome 3q27, a locus correlated with metabolic syndrome, whereas, apM1polymorphismspromoting the inhibition of adiponectin production were identified in individuals with insulin resistance (Kissebah et al, 2000). Particularly, serum adiponectin concentration in pre-diabetic conditions determined the development of type 2 diabetes mellitus. By contrast, reduction of body weight and therapy with thiazolidinediones were accompanied by increase of adiponectin suggesting that the latter could be a potent marker of metabolic syndrome (Maeda et al, 2001; Mather et al, 2008).

Finally, hypoadiponectinemia was found correlated with conditions associated with insulin resistance, such as both alcoholic and no-alcoholic adipose liver disease chronic hepatitis C, and polycystic ovary syndrome (Sato et al, 2005; Youet al, 2005; Tanet al, 2006; Tsochatzis et al, 2006).

The sex- and geographical region-oriented differences in adiponectin levels are not yet fully understood, however, the role of androgens or other confounders (e.g. central type obesity in men, different level of insulin resistance)could at least partly explain that phenomenon (Combset al, 2003; Isobeet al, 2005; Kadowakiet al, 2006; Renaldy et al, 2009).

Correlation between ghrelin/adiponectin and obesity

As previously discussed ghrelin has a potent orexigenic effect, stimulating AGRP(Agouti-Related Protein), NPY (Hypothalamic Neurons Neuropeptide), orexin A and B. Ghrelin counteracts the anorexigenic effects of leptin at central nervoussystem (CNS). Ghrelin's levels reach their peak concentration during fasting, whereas caloric intake produces a fall in the serum ghrelin (Pinkney & Williams, 2002).

It is proved that externally administrating high levels of ghrelin can cause stable increase of food intake, leading to increasing weight. The secretion rate makes ghrelin responsible for the immediate increase of thesense of hungry, given that it is increased in the highest levels few minute before the meal and is decreased in the lowest levels after the end of the meal (Cummings et al, 2002; Shiiyaet al, 2002). Obesity is connected with low levels of ghrelin in plasma, whereas the anorexia nervosa is associatedwith high levels.

It stimulates pre-adipocyte differentiation, increases the body fat and inhibits the anorexigenic effect of leptin. After gastric bypass surgery, ghrelin's levels are staidly reduced with simultaneous disorder of the secretion rate. The latter might beattributed to thelossof important number of gastric cells which produce the hormone. In case of bulimia, ghrelin's levels were found to be increased even in persons with normal body mass, probably due to abnormal habits of food intake, putting the suspicion for participation of ghrelin to this disorder (Caminoset al, 2002; Cummings et al, 2002).

In patients with cachexia the administration of ghrelin is correlated with increasing food intake andsimultaneous weightgain (Nagaya et al, 2001; Tanaka et al, 2002). It is also observed that ghrelin's levels are increased in hypothyroidism, whereas their levels are decreased in hyperthyroidism (Caminoset al, 2002).

Adiponectin serum levels are significantly reduced in central obesity. Although the adiponectin is produced exclusively by the antipocytes, mechanisms of negative regression feedback, cause reduction of its concentration in obesity, unlike the other adiponectines (Nagaya et al, 2001; Berg et al, 2002; Cnop et al, 2003; Takemuraet al, 2007; Komura et al, 2010).

Correlation between ghrelin/ adiponectin and cardiovascular diseases

Ghrelin's receptors have been isolated in whole cardiovascular system. Their concentration found increased in patients with atherosclerosis, coronary heart disease and other vascular diseases. External administration of ghrelin in patients with congestive heart was accompanied by reduction of arterial blood pressure (Kojima & Kangawa, 2005; Zhang et al, 2010), increase of cardiac index and stroke volume without changes in the mean pulmonary pressure. Beneficial results such as improvement of left ventricular function were also documented in animal models due to the reduction of peripheral arterial resistance.

Increased accumulation of the des-acyl ghrelin (inactive form of the hormone) but not of the total ghrelin in plasma, it observed also in patients with renal failure. This increase is connected with creatinine levels. Accordingly, the kidneys have an important role to the clearance and metabolism of des-acyl ghrelin.

In the course of normal pregnanciesghrelin levels are negatively correlated with blood pressure, whereas in hypertensive pregnancies ghrelin levels are high (Bodartet al, 1999; Iglesiaset al, 2004; Zhang et al, 2010).

As previously discussed ghrelin administration is associated with decreased systemic vascular resistance whereas increases the cardiac output in patients with heart failure and in healthy individuals and improves the heart structure and function. In animal models of heart failure, ghrelin administration improves cardiac contractility and attenuates the development of cardiac cachexia.

Recent studies demonstrated the anti-apoptotic effect of ghrelin in myocardium cells in the context of both ischemic heart failure and anthracycline-induced cardiomyopathy. Additionally, ghrelin

attenuates atherosclerotic progression, both by modulation of inflammatory processes and by inhibition of leucocytes chemoattractant properties.

These effects might mediate the possible protective role of ghrelin and its synthetic secretagogoues on cardiovascular system (Muccioli et al, 2000;Wiley & Davenport, 2002; Cao et al, 2006).

At present many clinical studies indicate that adiponectin could have a protective effect against the development of cardiovascular diseases (Frystyk et al, 2007) through its anti-inflammatory effects. In vivo studies in mice confirmed the anti-atherogenic properties of adiponectin previously (Matsuda et al, 2002; Verma et al, 2004).

Adiponectin deficient mice demonstrated enhanced thrombus formation and platelet aggregation at sites of vascular injury as compared with their controlled counterparts (Kato et al, 2006) suggesting that adiponectin may possess potential antithrombotic properties.

Adiponectin has also been shown to: stimulate the productionof nitric oxide (NO) in vascular endothelial cells; inhibitthe expression of adhesion molecules; inhibit class A scavengerreceptor expression in macrophages; and inhibit proliferationand migration of human aortic smooth muscle cells (Hug & Lodish, 2005; Trujillo & Scherer, 2005).

Hypoadiponectinemia appears to be associated with peripheral arterial disease. Low plasma levels of adiponectin were associated with the presence of symptomatic peripheral arterial disease, independent of traditional risk factors (Dieplinger et al, 2006). However, the same inverse relationship was not detected in patients with chronic heart failure. Low concentrations of adiponectin appear to be associated also with an early onset of coronary heart disease and the presence of multiple atherosclerotic lesions on coronary arteries.

The association of hypoadiponectinemia with atherosclerotic disease extends beyond the coronary vasculature. In a case-control study among individuals with or without ischemic cerebrovascular disease, decreasing concentrations of adiponectin were independently and significantly associated with a higher risk of stroke (Chen et al, 2003).

Lower concentrations of plasma adiponectin have also been associated with both essential hypertension and dyslipidemia. Patients with essential hypertension appear to have significantly lower levels of plasma adiponectin compared to normotensive patients.

A correlation between adiponectin and HDL-cholesterol, triglycerides and NT-pro brain natriuretic peptide(BNP), was also observed after adjustment for multiple confounders suggesting that dyslipidemia could be an intermediate link between adiponectin and atherosclerosis progression (Chen et al, 2003; Shibata et al, 2004; Dieplinger et al, 2006).

Adiponectin “paradox” in the setting of heart failure (HF) progression: in HF the increase of the adiponectin levels, associated to the decrease in body weight, have not the waited cardiovascular protective actions. High adiponectin levels act as indicators of disease severity, but its function as pathophysiological mediator is less relevant in this situation suggesting the existence of a “functional adiponectin resistance” in HF.

Adiponectin may serve to limit cardiac remodeling, which leads to hypertrophy and diastolic dysfunction, as well as to provide protection from ischemic damage. In adiponectin deficient mice, pressure overload resulted in enhanced concentric cardiac hypertrophy and increased mortality compared to control mice (Shibata et al, 2004).

Conclusions

An initial interest about ghrelin can be attributed to the ability of ghrelin to stimulate feeding in mammals suggesting it as a potential target for the development of anti-obesity drugs. It has been also proved that ghrelin participates with the GHRH (Growth hormone releasing hormone) and the somatostatin to the regulation of the GH production in the pituitary. Ghrelin is an

important factor influencing growth hormone release during pregnancy too.

The integrative role of ghrelin in homeostatic regulation is evident from its function in the regulation of reproduction versus feeding.

Ghrelin inhibits the activity of the hypothalamic-pituitary-gonadal axis acting both centrally and peripherally, similar to hypothalamic neuropeptide Y (NPY), and a down-stream target of ghrelin. It has been found to increase plasma epinephrine levels in humans, suggesting that it may also inhibit insulin secretion via a sympathetic response.

The ghrelin receptors density concentration has found increased in patients with atherosclerosis, coronary heart disease and other vascular diseases. It has also found that the external administration of ghrelin in patients with congestive heart disease caused positive effects, as reduction of arterial blood pressure without changes of cardiac rate. The adipose tissue does not only store excess of energy, but adipokines also, which are responsible directly and indirectly for the cardiac homeostasis. The adiponectin has a role of mediator in insulin's action as well as a strong ant inflammatory and anti atherogenic action.

The majority of studies have shown the adiponectin's serum concentration is a biological base of diabetes prevention as well as dyslipidemia, hypertension, which are significant factors for cardiovascular disease. The sex, age, nationality, the central obesity hereditary factors affect adiponectin's concentration levels, which are inversionally associated with the adipose mass and the insulin resistance. Its action to the central nervous system increases the energy expenditure and fatty acids oxidation.

Further studies will specify the accurate results and the action mechanisms of adiponectin in order to facilitate the clinical practice. Further studies also are needed to clarify the role of these peptides and to add a new knowledge in international scientific community.

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